REMARKS

The Claim Amendments

Claim 1 has been amended such that each occurrence of R′ is independently hydrogen or an optionally substituted C_{1-6} aliphatic group, or a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Support for this amendment is in the claim as originally filed.

Claims 54-57 have been amended to recite methods of treating various diseases or disorders using a compound of claim 1. Support for these amendments is found in paragraph [00135] on page 100 of the specification.

The Response

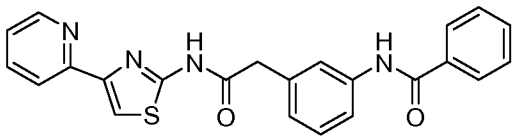
Rejection under 35 U.S.C. § 112, second paragraph

The Examiner has rejected claims 54-57 under U.S.C. § 112, second paragraph for allegedly failing to particularly point out and distinctly claim the subject matter. In particular, the Examiner asserts that the nature of the recited compositions is not clear. Claims 54-57 have been amended to recite methods of using compounds of the invention in the treatment of various diseases or disorders, thus obviating the rejection. Accordingly, applicants respectfully request that the Examiner withdraw the rejection of claims 54-57 under U.S.C. § 112, second paragraph.

Rejection under 35 U.S.C. § 102(b)

The Examiner has rejected claims 54-57 under 35 U.S.C. § 102(b) as allegedly being anticipated by Inaba et al., Japanese Patent Application No. 2002053566 (hereafter, "Inaba"). In particular, the Examiner asserts that Inaba teaches several thiazole compounds useful for treating Alzheimer's disease and allergy (i.e., Compounds 51 and 80 on pages 35 and 42, respectively) that fall within the scope of the rejected claims. Applicants traverse in part.

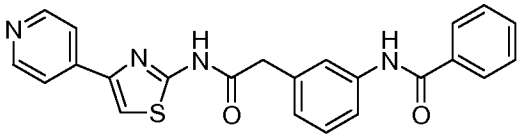
The structure of Compound 51 of Inaba is shown below.



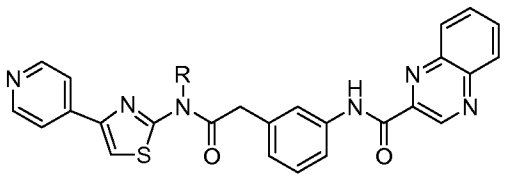
Compound 51

Since compound 51 is a thiazole linked to a pyridin-2-yl ring and the compounds of the invention are thiazoles linked to pyridine-4-yl moieties, the rejection over compound 51 is obviated.

As for the rejection over Compound 80 of Inaba, applicants have amended claim 54 to recite methods of using the compounds of claim 1 for treating various diseases/disorders. Claim 1 disclaims compound 80, thus obviating the rejection. In addition to Compound 80, applicants note that Compounds 44, 113, and 114 are the only other thiazoles exemplified by Inaba that are linked to a pyridin-4-yl ring. See below for the structures of these compounds. Compound 44 is also disclaimed in claim 1 and Compounds 113 and 114 do not fall within the scope of the amended claim. For the above reasons, applicants respectfully request that the Examiner withdraw the rejection of claims 54-57 under 35 U.S.C. § 102(b).



Compound 44



Compound 113 (R is H)
Compound 114 (R is CH_3)

Rejection under 35 U.S.C. § 103(a)

The Examiner has rejected claims 1, 4, 5, 8-12, 14- 20, 23-29, 31, 33-46, and 54-57 under 35 U.S.C. § 103(a) for allegedly being obvious in view of Inaba. In particular,

the Examiner asserts that the compounds of Inaba are kinase inhibitors useful for the treatment of Alzheimer's disease and allergy and that some of the compounds of Inaba are positional isomers of the compounds of the present invention, therefore making the compounds of the present invention not patentably distinct. Applicants traverse.

When establishing the differences between the prior art and the present invention in the obviousness rejection, the Examiner states that Inaba describes compounds that are useful for the treatment of Alzheimer's and allergy. However, applicants are unable to find the relevant descriptive text in Inaba that relates to the treatment of these diseases by the compounds therein. According to the Manual of Patent Examining Procedure (MPEP) § 707.07, "[i]n citing foreign published applications or patents, in case only a part of the document is involved, the particular pages and sheets containing the parts relied upon will be identified."). In contrast to the assertion by the Examiner, an English language translation of the abstract of Inaba provided by Chemical Abstracts Service indicates that the compounds of Inaba were prepared as sedatives. The translation is as follows:

> Protein kinase C inhibitors contain thiazole compds. I [R^1 = H, halo, C_{1-6} alkyl; R^2 = H, (un)substituted C_{1-6} alkyl (substituents are given); R^3, R^4 = H, (un)substituted C_{1-6} alkyl, ORa1 (Ra^1 = H, C_{1-6} alkyl, C_{1-6} alkylcarbonyl), $NR^{a2}R^{a3}$ (R^{a2}, R^{a3} = H, C_{1-6} alkyl, C_{1-6} alkoxycarbonyl); $NR^{a2}R^{a3}$ may be a ring; R^2 and R^3 may be bonded together with $NCOCR^4$ to form a (hetero)cycle; X = direct bond, C_{1-4} alkylene, O, S, CO_2, OCO, NR^{a4}, $CONR^{a4}$, $NR^{a4}CO$ [R^{a4} = H, (un)substituted C_{1-6} alkyl]; ring Hy = (un)substituted heterocyclyl containing 1-4 O, N, and/or S; Z = H, (un)substituted C_{1-6} alkyl, C_{6-14} aryl, C_{3-7} cycloalkyl, C_{3-7} cycloalkenyl, heterocyclyl; ring Cy = C_{6-14} aryl, C_{3-7} cycloalkyl, heterocyclyl] or their pharmaceutically acceptable salts. Drug compns. and sedatives containing I or their salts are also claimed. I selectively inhibit protein kinase C g-isoenzyme. IC_{50} values of N-[4-[2-(cyclopropylcarbonylamino)-4-methylthiazol-5-yl]thiazol-2-yl]-N-[2-(dimethylamino)ethyl]-2-(2-fluorophenyl)acetamide (II, preparation given) to PKCα, PHCβII, and PKCγ were 0.8691, 2.9062, and 0.0369 mM, resp. Sedative effect of II was shown in formalin test for rats. Tablets containing II were also formulated.

The only biological data presented in Inaba show the *in vitro* inhibition of PKC isoforms by the compounds exemplified therein or their efficacy in an *in vivo* pain model. See pages 100-112 of Inaba. Since the compounds of the present invention are not described or claimed as sedatives or as PKC inhibitors, there is no nexus that relates the biological activity of the compounds of Inaba to the compounds of the present invention.

The Examiner also asserts that the compounds of Inaba are closely related positional isomers of the compounds of the present invention and that it would have been obvious to one skilled in the art at the time the invention was made to expect the compounds of the present invention to possess the utility taught by the compounds of Inaba. Of the 306 compounds that are exemplified in Inaba, only 7 (compounds 44, 46, 51, 80, 82, 113, and 114) have a pyridyl substituent at the position that corresponds to the pyridin-4-yl substitutent of the compounds of the present invention. Biological data are proffered for only 2 of these 7 compounds (compounds 44 and 113) and in each case, the PKC inhibition demonstrated is less than that of other compounds of Inaba for which data were reported. Accordingly, Inaba teaches away from the preparation or use of the pyridin-4-yl thiazoles of the present invention as kinase inhibitors.

Furthermore, in order to find a *prima facie* case of unpatentability in instances where close or established structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds, "a showing that the prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention [is] also required." See *Takeda v. Alphapharm* (Fed. Cir. 2007), citing *In re Jones* (Fed. Cir. 1992); *In re Dillon* (Fed. Cir. 1990), *In re Grabiak* (Fed. Cir. 1985), and *In re Lalu* (Fed. Cir. 1984). "Thus, in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish *prima facie* obviousness of a new claimed compound" (emphasis added). See *Takeda v. Alphapharm*. As mentioned previously, there is no nexus that relates the

biological activity of the compounds of Inaba to the compounds of the present invention. Further, the vast majority of the compounds exemplified by Inaba (300 out of 307) do not contain a pyridyl substitutent that corresponds to the 4-pyridyl substituent of the compounds of the present invention. Further still, the biological activities reported for those Inaba compounds that do contain such a pyridyl substituent are not superior to those Inaba compounds that do not contain such a substituent. Accordingly, nothing in Inaba provides a suggestion or motivation to prepare the pyridine-4-yl compounds of the present invention.

For the reasons presented above, applicants respectfully request that the Examiner withdraw the rejections of claims 1, 4, 5, 8-12, 14- 20, 23-29, 31, 33-46, and 54-57 under 35 U.S.C. § 103(a).

Conclusion

Applicants request that the Examiner enter the above amendments, consider the accompanying arguments, and allow the claims to pass to issue. Should the Examiner deem expedient a telephone discussion to further the prosecution of the above application, applicants request that the undersigned be contacted at the Examiner's convenience.

Respectfully submitted,

/Daniel A. Pearson/

Daniel A. Pearson (Reg. No. 58,053)
Agent for Applicants
c/o Vertex Pharmaceuticals Incorporated
130 Waverly Street
Cambridge, MA 02139-4242
Tel.: (617) 444-6790
Fax.: (617) 444-6483